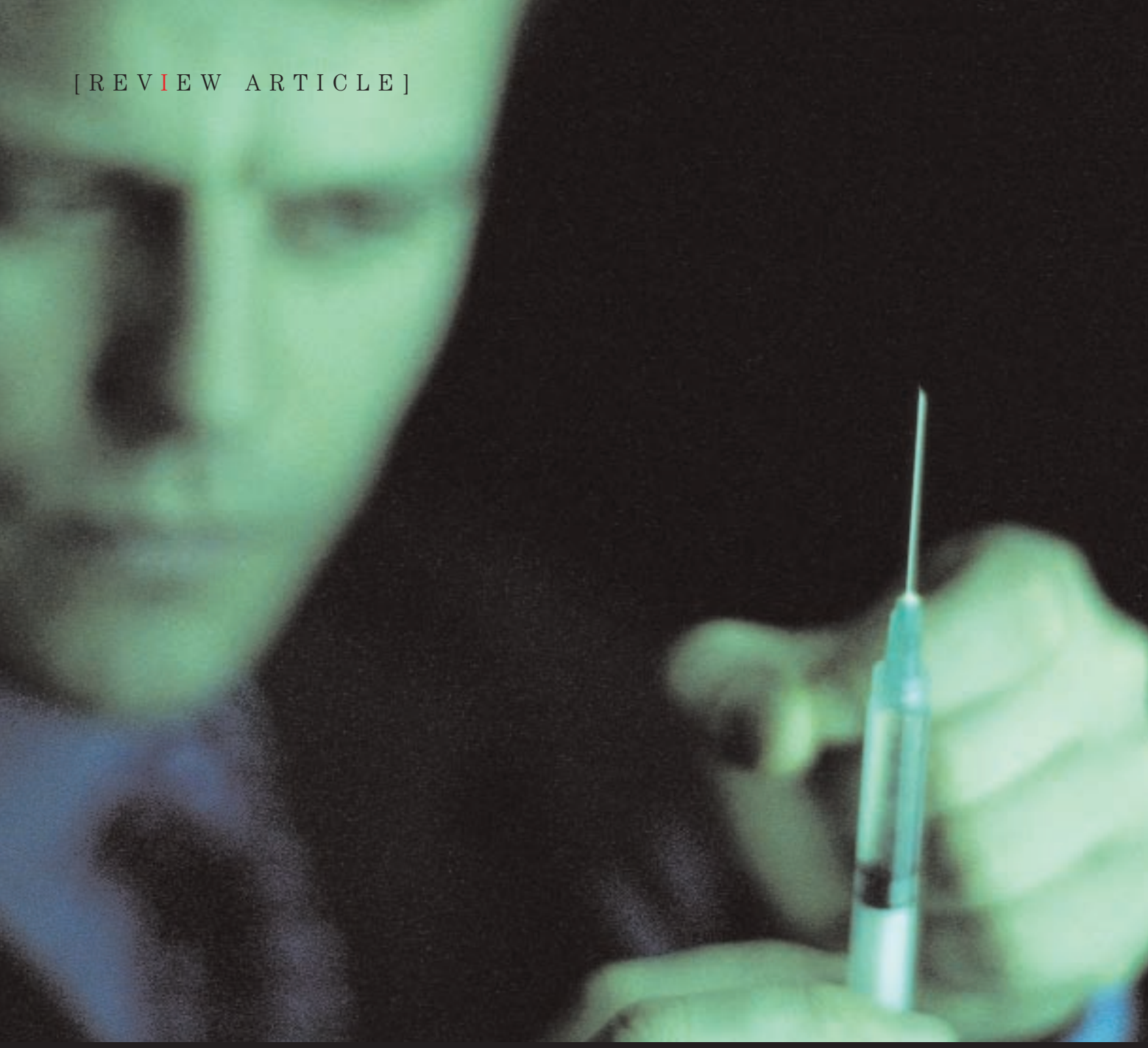

EVIDENCE-BASED ADDICTION MEDICINE

The Use of Lofexidine for Opioid Detoxification

Is there any evidence that lofexidine is as effective as and better tolerated than clonidine for opiate detoxification? Could lofexidine be safely combined with other agents in the management of withdrawal? The purpose of this review is to seek answers to these postulates by using evidence-based testimony.

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Dependence on opioid drugs is a major health and social issue in most societies, including the United States. The intolerable symptoms associated with abstinence significantly contribute to the high rates of relapse.[1,2] The signs and symptoms of the opioid withdrawal syndrome include irritability, anxiety, apprehension, muscular and abdominal pains, chills, nausea, diarrhea, yawning, lacrimation, sweating, sneezing, rhinorrhea, general weakness, and insomnia. These symptoms start between 6 and 48 hours after last usage depending on the half-life of the opioid.[3] Ability to manage these withdrawal symptoms is thus essential to an effective treatment.

Due to its high oral bioavailability and longer half life, methadone has traditionally been used to treat such withdrawals. However, the limitations to its use include its protracted withdrawal symptoms, as well as the paradox of using a drug of dependence to treat opiate dependence. The emergence of clonidine then provided a non-opioid alternative to the management of opioid withdrawal.

Even though there is no consensus on the best approach to the management of withdrawal symptoms,[4] clonidine became the unofficial gold standard alpha-agonist agent for opiate detoxification. In recent years, however, the use of its structural analogue, lofexidine, has gained momentum. Licensed for use in the United Kingdom[5] in 1992, it may soon be welcomed to the armamentarium of opiate and alcohol detoxification in the United States.[6]

Like clonidine, its mechanism of action relates to inhibition of noradrenergic activity through presynaptic stimulation of alpha-2-adrenergic neurons. By so doing, it counteracts the anxietogenic effects that make opiate withdrawal so unbearable. The attraction toward the use of lofexidine is the possibility that while it may be at least as effective as clonidine in the management of opiate withdrawal, it does not have the major limitation of postural hypotension. Is there any evidence that lofexidine is as effective as and better tolerated than clonidine for opiate detoxification? Could lofexidine be safely combined with other agents in the management of withdrawal? The purpose of this review is to seek answers to these postulates by using evidence-based testimony.

THE QUESTION

Does lofexidine play a significant role in the management of opiate detoxification to warrant its license in the United States, thus serving as a useful alternative to clonidine? Can it be safely combined with other agents in the management of opioid withdrawal symptoms?

THE ANALYSIS

Using Pubmed (www.pubmed.gov)

The query keyed into the subject search relates to lofexidine in opiate detoxification.

THE EVIDENCE

Prior to the comparison with clonidine, how would the new agent fare against the more traditional methadone replacement? In 1996, Bearn, et al.,[7] conducted a randomized, double-blind, controlled comparison of lofexidine and methadone for the treatment of opiate withdrawal in 86 patients. They found that lofexidine was broadly clinically equivalent to methadone and appeared to be a non-opiate treatment of opiate withdrawal without the serious limiting hypotensive side effects.

The following year at an addictive behavior center in Birmingham, England, Khan and his co-workers[8] conducted a double-blind, randomized study on 28 opiate-addicted patients who had hitherto been stabilized on methadone. The patients were randomized into lofexidine and clonidine groups, and researchers found that the withdrawal course was similar in both groups, but with significant reduction in side effects and hypotension for those on lofexidine. In the same year, Lin and colleagues in Taiwan conducted a study on 80 hospitalized heroin addicts. These patients were randomized into lofexidine- or clonidine-treatment groups during detoxification. The researchers found that while both medications were equally effective, the lofexidine group had better treatment retention rates due to fewer hypotensive problems.

In 1998, Brown and Fleming[10] conducted a naturalistic home detoxification study using lofexidine. They found that while lofexidine appeared to be a useful treatment for some opiate-dependent individuals, it is more successful in those whose drug use is already well controlled.[10]

Though only a few studies have evaluated the effectiveness of combining lofexidine with other agents, the results of such combinations point toward a faster and more sustained resolution of withdrawal symptoms.

In 1999, Akhurst[11] of Britannia Pharmaceuticals in England collected data on 1,074 lofexidine-opiate detoxifications from 40 drug dependency units in the United Kingdom. About two thirds of these patients were community based, while the remaining third were in-patients. The study concluded that lofexidine was useful in rapidly detoxifying patients from a range of opiates.

In 2002, Howells and colleagues[12] published a prison-based study using lofexidine in a prison setting. The study was randomized and conducted as a double-blind trial with methadone as its control. The study did not discern any statistical difference between the treatment groups in terms of the severity of withdrawal symptoms, blood pressure, and heart rate measurement. This showed that lofexidine compared well not only to clonidine, but to methadone as well.

In comparison with methadone, Beswick, et al.,[13] found in 2003 that reduced sleep disturbance is yet another advantage of lofexidine detoxification regimen. The self-report nature of the study lends itself to its own methodological flaw, but in general patients on methadone protocol reported lower overall sleep, longer sleep latencies, and longer periods of time awake than lofexidine patients. Not all of the studies were expressively positive about lofexidine. Walsh, et al.,[14] conducted a randomized study, implementing subject crossover design and with drug administration taking place under double-blind and triple dummy conditions. They examined the efficacy of lofexidine to suppress opioid withdrawal symptoms in patient laboratory conditions using a naloxone challenge procedure. Lofexidine was compared to placebo and clonidine. Lofexidine and clonidine both produced dose-related decreases in blood pressure and heart rate. Significantly, neither lofexidine nor clonidine suppressed the subjective discomfort of opioid withdrawal or significantly reduced other autonomic signs of opioid withdrawal, such as lacrimation or rhinorrhea. Based on these findings, they concluded that lofexidine's failure to modify most signs and symptoms of opioid withdrawal suggest that its effective use in spontaneous withdrawal will require concomitant medica-

tions for improved therapeutic response.

THE QUESTION

Is lofexidine useful in rapid detoxification?

THE EVIDENCE

In 1998, Bearn, et al.,[15] found that an accelerated five-day lofexidine regimen may attenuate opiate withdrawal symptoms more rapidly than conventional 10-day lofexidine or methadone treatment schedules without exacerbating hypotensive side effects. When their group joined Buntwal[16] in a study combining naltrexone and lofexidine together, they found that the naltrexone/lofexidine combination was associated with a more rapid resolution of the opiate withdrawal syndrome than a seven-day lofexidine-only treatment schedule, without substantial increases in withdrawal symptoms or hypotensive side-effects. Still, on the subject of rapid detoxification, Gerra, et al.,[17] also found that lofexidine appeared to be more useful than clonidine in a three-day accelerated opiate detoxification, not only in counteracting withdrawal symptoms but also in the treatment of dysphoria and mood changes. As with other studies, they also found that lofexidine does not produce hypotension, reflecting a better safety profile when used in outpatient settings.

THE QUESTION

Can lofexidine be safely combined with other medications to achieve opiate detoxification?

THE EVIDENCE

In 2000, Buntwal, et al.,[16] compared a combination of lofexidine and naltrexone with lofexidine alone in a study of 22 opiate-dependent patients. Withdrawal symptoms were found to not only be significantly less in the combination group, but there was additionally a faster resolution of the withdrawal syndrome than when lofexidine alone was used.[16] Both treatment groups had similar minimal effects on blood pressure.

In 2003, Beswick, et al., carried out a double-blind randomized and placebo-controlled trial at the National Addiction Centre in London, and compared the effectiveness of combined naloxone/lofexidine with lofexidine/placebo in 89 opiate-dependent patients. Patients in the combination group demonstrated a more gradual reduction in the level of withdrawal and craving. Also, at completion those patients maintained a level of withdrawal consistently lower than the lofexidine/placebo group.[3]

CONCLUSION

Based on the studies above, one can conclude that lofexidine, a non-opiate, non-addictive alpha-2-agonist, would be a useful addition to the armory used by addiction physicians in the United States. The relative safety profile of lofexidine as compared to that of clonidine would make it useful in a variety of settings, especially in the setting of outpatients. Though only a few studies have evaluated the effectiveness of combining lofexidine with other agents, the results of such combinations point toward a faster and more sustained resolution of withdrawal syndromes. The bottom line is that in the addiction specialty, there is a degree of welcoming enthusiasm about the impending clinical trials of this useful agent in the United States.

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